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Research report

Cortical negative motor network in comparison with sensorimotor network: A cortico-cortical evoked potential study

Rei Enatsu [a], Riki Matsumoto [d], Zhe Piao [a], Timothy O'Connor [a], Karl Horning [a], Richard C. Burgess [a,b], Juan Bulacio [a], William Bingaman [a,c] and Dileep R. Nair [a,b,*]

[a] Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH, USA
[b] Department of Neurology, Cleveland Clinic Foundation, Cleveland, OH, USA
[c] Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH, USA
[d] Department of Neurology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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ABSTRACT

The purpose of this study was to investigate the connectivity from the negative motor area and to elucidate the mechanism of negative motor phenomena. We report the results of cortico-cortical evoked potentials (CCEPs) by electrical stimulation of the primary motor area (MI), primary sensory area (SI), primary (PNMA) and supplementary negative motor area (SNMA) in eight epilepsy patients who underwent intracranial electrode placement. Alternating 1-Hz electrical stimuli were delivered to MI (six patients), SI (five), PNMA (six) and SNMA (two). CCEPs were recorded by averaging electrocorticograms time-locked to the stimuli. Stimulation of MI, SI and PNMA induced CCEP responses in the premotor area (PM), pre- and postcentral gyri, posterior parietal cortex and the temporo-parietal junction. Upon SNMA stimulation, CCEP responses were detected in the prefrontal cortex, PM, pre- and postcentral gyri, supplementary motor area (SMA) and preSMA. Compared with stimulation of SI and MI, PNMA stimulation revealed a broader distribution of CCEP responses in the frontal or parietal association cortex, indicating the importance of the fronto-parietal network associated with a higher level of motor control. We concluded that these connections are associated with motor control and that the negative motor phenomenon results from impairment of the organization of movements.

1. Introduction

Penfield and Jasper (1954) and later Lüders et al. (1988) reported that electrical stimulation of a certain cortical area in the frontal lobe elicited the arrest of voluntary movements. This cortical area was named the negative motor area (NMA) because of the characteristic phenomenon called the negative motor response (Lüders et al., 1988, 1995; Smyth, 2008; Filevich et al., 2012). Negative motor response is defined as the inability to continue voluntary movements or sustained muscle

* *Corresponding author*. Epilepsy Center, Cleveland Clinic, S51 9500 Euclid Avenue, Cleveland, OH 44195, USA.
E-mail address: nairdr@ccf.org (D.R. Nair).
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contraction without disturbance of consciousness (Lüders et al., 1988, 1992, 1995; Smyth, 2008; Filevich et al., 2012). NMA in humans is identified in the lateral frontal area just rostral to the primary face motor area (primary NMA – PNMA), and in the medial frontal area just rostral to the supplementary motor area (SMA) proper (supplementary NMA – SNMA) (Lüders et al., 1988, 1992, 1995; Smyth, 2008). Negative or inhibitory motor phenomena have attracted increasing attention in clinical neurology because they are related directly not only to the pathophysiology of neurological disorders such as inhibitory seizures (Satow et al., 2002; Ikeda et al., 2009), but also to higher motor control in humans (Lüders et al., 1995; Kunieda et al., 2004); however, the neurophysiological mechanisms governing negative motor responses remain unknown.

The precise definition of the connectivity associated with NMA is essential to better understand the complex functional organization of negative motor phenomena. *In vivo* human brain connectivity studies have only recently begun using non-invasive methods, such as diffusion tensor imaging (Catani et al., 2002, 2012; Jones, 2008; Mukherjee et al., 2008). This technique, however, cannot provide details of functional aspects of the brain, i.e., cortical functions and functional connectivity among cortical regions. It would be optimal if both functional cortical regions and their white matter connections could be mapped within the same subject, so as to be able to track exact neuronal connections.

In vivo single-pulse electrical stimulation was recently introduced in humans to track the various brain networks (Coleshill et al., 2004; Greenlee et al., 2007; Lacruz et al., 2007, 2010; Oya et al., 2007; Rosenberg et al., 2009; Keller et al., 2011) and evaluate the cortical epileptogenicity (Valentin et al., 2002, 2005a, 2005b; Flanagan et al., 2009). Cortico-cortical evoked potentials (CCEPs) are obtained by averaging responses time-locked to electrical stimuli. This invasive tract-tracing method provides an opportunity to track connectivity among various functional areas that can be defined by cortical electrical stimulation and magnetic resonance imaging (MRI)-electrode co-registration (Matsumoto et al., 2004, 2007, 2011; Terada et al., 2008, 2012; Umeoka et al., 2009; Kikuchi et al., 2012; Koubeissi et al., 2012) and to evaluate the cortical excitability at and around the epileptic focus (Matsumoto et al., 2005; Iwasaki et al., 2010; Enatsu et al., 2012). By means of CCEP, we report here the connectivity pattern of NMA in comparison with that of the primary sensorimotor area in patients with intractable epilepsy.

2. Patients and methods

2.1. Patients

Eight patients were studied who had undergone chronic intracranial electrode placement for the presurgical evaluation of medically intractable partial epilepsy (Table 1). One patient (Patient 1) is left handed and seven patients (Patient 2–8) are right handed. All patients had subdural electrodes placed over the lateral convexity of the frontal and parietal lobe and three also had depth electrode implantation (Patient 2, 4 and 8). Patient 2 had four depth electrodes in the left amygdale (electrode "LAM"), anterior hippocampus (electrode "LAH"), posterior hippocampus (electrode "LPH") and posterior cingulate (electrode "LPC"). Patient 4 had two depth electrodes: one in the left hippocampus (electrode "LH") and another in the left insula (electrode "LI"). Patient 8 had four depth electrodes in the right superior frontal gyrus (electrode "FA" and "FC"), middle frontal gyrus (electrode "FB") and postcentral sulcus (electrode "PA"). The subdural electrodes were made of platinum and measured 3.97 mm in diameter with a center–center inter-electrode distance of 1 cm (custom-made at Cleveland Clinic Foundation, OH). Depth electrodes were made of platinum 2.5 mm contacts with a 2.5 mm gap and a diameter of 1.25 mm (Integra, Plainsboro, NJ).

The study was performed extraoperatively after the standard presurgical evaluation and restarting antiepileptic medications. The relationship of the electrode position to major cerebral sulci was identified on a presurgical three-dimensionally reconstructed MRI image coordinated with post-operative high resolution volumetric computed tomography (CT) (1 mm slice thickness) (Ray et al., 2007; Nair et al., 2008). This coordination was performed using the in-house program (Vamis; program developed by Cleveland Clinic Foundation, OH). The present study was approved by the Institutional Review Board Committee of Cleveland Clinic Foundation, and informed consent was obtained from all patients (IRB #4513).

2.2. Functional and anatomical brain mapping

Cortical electrical stimulation was performed for functional mapping as part of the routine presurgical evaluation. Repetitive square wave electrical currents of alternating polarity with a pulse width of .3 msec were delivered at a frequency of 50 Hz for 2–5 sec (Grass S-88 and SUI-7; Astro-Med Inc., West Warwick, RI) (Lüders et al., 1988). Positive motor and sensory areas were identified by a positive motor response (muscle twitch) and subjective sensory sensation, respectively. Both the caudal Brodmann area (BA) 6 and BA4 have a direct corticospinal pathway and stimulation of both areas elicits positive motor responses (Rizzolatti et al., 1998; Tanner and Lüders, 2008). It is therefore physiologically difficult to identify the border between BA6 and BA4 by cortical electrical stimulation on the crown of the precentral gyrus. Therefore, in the present study, we refer to the positive motor area on the precentral gyrus as the primary motor area (MI). We also classified the positive sensory area on the postcentral gyrus as the primary sensory area (SI). Hand NMA was defined as the region which, upon cortical stimulation (50 Hz, 5 sec) elicited cessation or slowing of the finger tapping (typically more impairment contralateral to the side of stimulation). Tongue NMA was defined as the region which, upon cortical stimulation elicited cessation or slowing of the rapid alternating movements of tongue. NMA on the lateral and medial brain surface in the frontal lobe was defined as the PNMA and SNMA, respectively (Lüders et al., 1988, 1992, 1995; Smyth, 2008). The premotor area (PM), SMA and preSMA were defined according to the previous proposal (Freund, 1996; Matsumoto et al., 2007). PM covers the dorsolateral aspect of the hemisphere at the front of the precentral sulcus (Freund, 1996). The rostral border of PM was defined 30–35, 15–30